National PBM Drug Monograph
Inhaled insulin (Exubera®)

VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

EXECUTIVE SUMMARY

Exubera is the first inhaled insulin (INH) to be approved by the FDA. It will be available to patients by September 2006. It is formulated as a dry powder and must be used with the Exubera inhaler.

Efficacy

There are two published 24-week non-inferiority trials in patients with type 1 diabetes. One compared INH before meals + ultralente at bedtime to regular insulin 2-3 times daily before meals + NPH twice daily. The other compared INH before meals + NPH twice daily to regular insulin before meals + twice daily NPH. Based on reduction in HbA1c, inhaled insulin was found to be non-inferior to regular insulin.

Several different comparators were used in the type 2 diabetes studies

- INH before meals vs. rosiglitazone 8mg in patients naïve to diabetes drug treatment (12-weeks).
  Treatment difference for HbA1c -0.89%[-1.23, -0.55]

- INH before meals + prestudy OHAs vs. INH alone before meals vs. prestudy OHAs alone in patients who were uncontrolled on oral combination therapy (12-weeks).
  Treatment difference for HbA1c -1.67% [-1.90, -1.44] for INH+OHA vs. OHA and **-1.18% [-1.41, -0.95] for INH vs. OHA**

- INH beforemeals + ultralente vs. mixed NPH/regular twice daily in patients previously receiving insulin and are not on OHAs (26-weeks).
  Treatment difference for HbA1c -0.07% [-0.32, 0.17]

- SU + INH vs. SU + metformin in patients previously on sulfonylureas (24-weeks). Results were stratified based on HbA1c at week 1.
  Treatment difference -0.38% [-0.63, -0.14] for high HbA1c stratum and **-0.07% [-0.33, 0.19] for low HbA1c stratum**

- Metformin + INH vs. metformin + SU in patients previously on metformin (24-weeks). Results were stratified based on HbA1c at week 1.
  Treatment difference -0.37% [-0.62, -0.12] for high hbA1c stratum and **0.04% [-0.19, 0.27] for low HbA1c stratum**

Safety

The rate of all hypoglycemia was slightly lower with INH + basal insulin compared to regular + NPH insulin in type 1 diabetes; however, the rate of severe hypoglycemia was higher with inhaled insulin.

In type 2 diabetes, the rate of all hypoglycemia was higher with inhaled insulin either in combination with OHAs or INH alone compared to OHAs alone. In the study comparing the combination of INH or regular insulin with NPH, the rate of all hypoglycemia was slightly slower in the INH group; however, the rate of severe hypoglycemia was slightly higher.

The majority of the studies showed a greater decrease in FEV1, FVC, and DLco for those groups receiving inhaled insulin. Change in FEV1 and DLco occur within the first several weeks of starting INH and do not progress over a 2-year treatment period. In patients with type 2 diabetes who were in the 2-year extension trial, it was shown that the treatment group difference in FEV1 resolved 6-weeks after discontinuing therapy with INH. Studies evaluating pulmonary function after discontinuing INH have not been conducted in patients with type 1 diabetes.

Baseline tests for lung function are recommended before beginning treatment and should be repeated after the first 6 months then annually thereafter. In patients that have a $\geq$ 20% decline in FEV1 from baseline,

pulmonary functions tests should be repeated. If a ≥ 20% decline in FEV1 is confirmed, inhaled insulin should be discontinued. For patients with lesser declines in FEV1, more frequent monitoring may be required and discontinuation of inhaled insulin considered.

Use of inhaled insulin is contraindicated in patients who smoke or who have recently quit smoking within the last 6 months of starting inhaled insulin. If smoking is resumed, inhaled insulin must be discontinued immediately, due to the increased risk of hypoglycemia. It is also contraindication in patients with unstable or poorly controlled lung disease.

Inhaled insulin is not recommended in patients with underlying lung disease such as asthma or COPD.

Because INH is dosed in milligrams and subcutaneous injected as units, there is a potential risk of dosing errors as patients and providers may confuse units and milligrams.

There is a potential risk for error as 3 x 1mg blisters are not equivalent to 1x 3mg blister

The inhaled insulin device and drug packaging may limit sufficiently fine adjustment of insulin dose.

INTRODUCTION
Exubera was approved by the FDA on January 27, 2006. Exubera will be available to patients in early September making it the first inhaled insulin (INH) to reach the market. Exubera is a dry-powder formulation of insulin. Other formulations, such as AERx®iDMS® are in various phases of clinical trials.

INDICATIONS
For control of hyperglycemia in adults with type 1 diabetes in conjunction with long-acting insulin and for adults with type 2 diabetes either as monotherapy, or in combination with oral agents or long-acting insulin.

PHARMCOKINETICS AND PHARMACODYNAMICS
It has been previously determined that the optimal size for particle delivery to the alveoli is 1-3µm in diameter. A fine, dry-powder formulation of regular human insulin < 5µm in aerodynamic diameter is delivered via the Exubera system. Insulin particles are transported by vesicles across the cell membrane of the alveolar epithelium. This packaged insulin is then transported through the alveolar capillary endothelium and released into the alveolar capillary bloodstream for absorption. Approximately 6-10% of inhaled insulin is absorbed systemically.

In a 3-way crossover study of healthy subjects (n=16), a single inhalation of Exubera 3mg, 3 inhalations of 1mg of Exubera, and 10units of subcutaneous regular insulin were compared.[1] Insulin concentration peaked earlier and decreased more rapidly after administration of inhaled insulin (both regimens) compared to injection. The plasma glucose concentration profile for both inhaled regimens was nearly superimposable. Compared to injected insulin, plasma glucose was slightly lower with inhaled insulin during the first hour after administration. From 60-300minutes post administration, the plasma glucose level was approximately 9mg/dl lower with injected insulin than inhaled insulin.

Using euglycemic glucose clamp techniques, the pharmacodynamic profile of Exubera 6mg, subcutaneous regular insulin 18 units, and subcutaneous insulin lispro 18 units were compared in non-smoking, non-diabetic subjects (n=17) in a 3-way crossover.[2] Euglycemic glucose clamp studies measures the glucose infusion rate (GIR) needed to maintain euglycemia after insulin is administered. The time to reach 50% of maximal GIR was 32, 48, and 41minutes for inhaled, regular, and lispro insulin respectively indicating that inhaled insulin has a faster onset of action. The maximal metabolic effect (GIRmax) was 8.7, 9.8 and 11.2mg/kg/min respectively. The duration of action was 387, 415, and 313 minutes respectively.

In the type 1 and 2 diabetes clinical trials, peak serum insulin concentration occurred in 49 minutes (range 30-90 minutes) with inhaled insulin and 105minutes (range 60-240minutes) with subcutaneous insulin.[30]

Within-subject variability was studied in 20 elderly obese patients with type 2 diabetes.[3] In a randomized 4-way crossover design, patients received a single dose of 4mg inhaled (twice on 2 separate days) and 12units subcutaneously (twice on 2 separate days) after an overnight fast. Serum free insulin Cmax and AUC_{0-2h} was approximately 1.8 times higher with inhaled insulin vs. subcutaneous, while AUC_{0-6h} was similar. Plasma glucose pharmacodynamics was consistent with the insulin kinetics (results not shown). There was little within-subject variability in insulin pharmacokinetics and glucose pharmacodynamics.

Special populations

There was no difference in pharmacokinetic properties of inhaled insulin with regards to gender and age > 65years and younger adults. Absorption of inhaled insulin is independent of body mass index.

In non-diabetic subjects with mild asthma, the absorption of INH was approximately 20% lower than in those without asthma. In contrast, the absorption of INH was 2-fold higher in non-diabetic subjects with COPD compared to those without COPD.[30]

EFFICACY

Type 1 diabetes (see Appendix 1)

There is one 12-week and two 24-week published trials in patients with type 1 diabetes with baseline HbA1c values between 6-11%. In the 12-week trial, Skyler et al. compared INH before meals + bedtime ultralente to patients who continued their usual regimen of twice daily NPH and regular insulin 2-3 times a day before meals.[4] Quattrin et al., conducted a 24-week study using the same dosing regimen as described above.[5] Skyler et al. also conducted a 24-week study that compared premeal INH + twice daily NPH to premeal regular insulin + twice daily NPH.[6] These studies were designed to show non-inferiority of regimens using INH to the comparator for the primary outcome of change in HbA1c.

In general, patients were excluded from study entry if they had poorly controlled asthma, other significant respiratory, renal, or cardiac disease, smoked in the last 6 months, significant insulin allergy, recurrent severe hypoglycemia, systemic glucocorticoid use or insulin pump use in past 2 months, insulin dose >150 units/day, hospitalization/ER visit due to poor diabetes control in past 6 months, or were pregnant.

Based on the dosing regimens described, HbA1c for inhaled insulin was found to be similar to regular insulin + NPH (table 1). In the 24-week studies, FPG and 2-hour post-prandial glucose were lower with inhaled insulin. The percentage of patients achieving HbA1c $\leq$ 7% and $\leq$ 8% were similar in both groups. (Refer to appendix 1)

Table 1: Change in HbA1c from published trials in patients with type 1 diabetes

	Duration	Treatment arms	Inhaled insulin	Comparator	Adjusted difference vs. control [95%CI]	% pts. achieving HbA1c < 7%
Skyler[4]	12-weeks	INH + ultralente vs. regular + NPH	-0.64%	-0.83%	0.2% [-0.2 to 0.5]	Not shown
Quattrin[5]	26-weeks	INH + ultralente vs. regular + NPH	-0.2%	-0.4%	0.16% [-0.01 to 0.32]	15.9%/ 15.5%
Skyler[6]	24-weeks	INH + NPH vs. regular + NPH	-0.3%	-0.1%	-0.16% [-0.34 to 0.01]	23.3%/ 22%

Type 2 Diabetes (see appendix 2)

Six trials evaluated INH in patients with type 2 diabetes. Mean baseline HbA1c ranged from 8.48 – 9.9%. In a 24-week non-inferiority trial, Hollander et al. compared premeal INH + bedtime ultralente to mixed regular/NPH administered twice daily in patients who had been on stable insulin injection regimens (no OHAs).[11] The remaining 5 trials evaluated INH +/- oral hypoglycemic agents (OHA). In a 12-week study, Weiss et al. compared the addition of premeal inhaled insulin to existing oral hypoglycemic agents (OHA) to OHA alone.[8] DeFronzo et al., compared 12-weeks of premeal INH to rosiglitazone 4mg BID in patients who were diabetes drug therapy naïve.[9] In another 12-week trial, Rosenstock et al. studied patients who were on dual therapy comprised of an insulin secretagogue and an insulin sensitizer. Patients were randomized to INH before meals in addition to their dual OHA, or premeal INH alone, or to continue their dual OHA.[10] Barnett compared the addition of INH or metformin to sulfonylureas in a 24-week trial.[33] Another 24-week trial (unpublished) compared the addition of INH or sulfonylurea to metformin.[30]

In general, patients were excluded from study entry if: BMI > 35mg/kg^2, had poorly controlled asthma, COPD, other significant respiratory disease, CHF requiring pharmacologic treatment, smoked in the last 6 months, abnormal EKG, DL_{CO} <75%, TLC <80% or >120%, FEV1 < 70% predicted., use of systemic steroids, ≥2 severe hypoglycemic episodes in past 6 months, hospitalization/ER visit due to poor diabetes control in past 6 months, pregnancy, other major disease, significant laboratory abnormalities.

In all studies, INH was administered within 10 minutes prior to meals. Patients received 1-2 inhalations of 1 or 3mg before meals. In general, initial INH doses were based on weight, meal size, time of day, recent or anticipated exercise (or baseline SQ insulin dose or previous insulin response in Hollander et al.). Dose can be increased or decreased by 1mg based on SMBG or in anticipation for meals that were larger or smaller than usual or on a PRN basis. Self-monitoring of blood glucose was performed before meals and at bedtime. Doses were adjusted to achieve target premeal glucose of 80-140mg/dL and bedtime value of 100-160mg/dL.

In all studies but one, the primary endpoint was mean change in HbA1c from baseline to end of study. In the DeFronzo study, the primary endpoint was the percentage of patients with HbA1c < 8%. In trials designed to show superiority, the intent-to-treat population was used with last observation carried forward approach. In the non-inferiority trials, the per-protocol population was used.

Results for HbA1c are shown in Table 2. The mean dose of inhaled insulin ranged from 12.7 - 26.4mg per day. Refer to appendix 2 for secondary efficacy outcomes such as fasting plasma glucose, post-prandial glucose, etc.

Table 2: Change in HbA1c from trials in patients with type 2 diabetes

	Duration	Treatment arms	Inhaled insulin	Comparator	Adjusted difference vs. control [95%CI]	% achieving HbA1c < 7% (INH/comparator)
Weiss[8]	12-weeks	INH + OHA vs. OHA	-2.3%	-0.1%	-2.2% [-2.7 to -1.7]	34%/ < 7%
DeFronzo[9]	12-weeks	INH vs. rosiglitazone	-2.3%	-1.4%	-0.89% [-1.23, -0.55]	44%/ 17.9%
Rosenstock[10]	12-weeks	INH + OHA vs. INH vs. OHA	-1.9% (INH+OHA) -1.4% (INH)	-0.2%	-1.67[-1.90, -1.44] -1.18[-1.41, -0.95]	32%/ 16.7%/ 1.0%
Hollander[11]	26-weeks	INH + ultralente vs. regular + NPH	-0.7%	-0.6%	-0.07% [-0.32, 0.17]	47%/ 32%
Barnett[33]	24-weeks	SU + INH vs. SU+ metformin	-2.2% (H) -1.9% (L)	-1.8% (H) -1.9% (L)	-0.38 [-0.63, -0.14] (H) -0.07 [-0.33, 0.19] (L)	20.4/ 14.6% (H) 30.7/32.3% (L)
Study 1002[30]	24-weeks	Metformin + INH vs. metformin + SU	-2.2% (H) -1.8% (L)	-1.9% (H) -1.9% (L)	-0.37 [-0.62, -0.12] (H) -0.04 [-0.19, 0.27] (L)	33.9/ 17.5% (H) 40/ 42.9% (L)

H = high stratum (baseline HbA1c >9.5 - ≤ 12.5%)
L = low stratum (baseline HbA1c ≥8% - ≤ 9.5%)

Long-term studies

The results of long-term studies are presented in table 3. Rosenstock et al., [12] reports the combined results of 1-year extension trials from the two parent 12-week trials by Cefalu et al and Skyler et al.[4, 7] Of the 118 patients from these 2 trials, 102 completed the 1-year extension. Among the patients randomized to inhaled insulin in the parent studies, 85% chose to continue treatment and 13.3% switched to subcutaneous (SQ) insulin. Among the patients randomized to SQ insulin in the parent studies, 21.3% chose to continue treatment and 75.4% switched to inhaled insulin. Change in HbA1c is shown in table 3.

Results of other long-term studies have been published in abstract form.

- Combined results from 1-year[13] and 2-year[34] extension trials (from the 24-week parent trials SU+INH vs. SU + metformin and metformin + INH vs. metformin + SU) are presented. During the extension, concomitant antidiabetic therapies were allowed. No details on these additional therapies were provided in the abstract.

- Cefalu presents 2-year efficacy and safety results in type 2 diabetes from an uncontrolled extension trial of 3 phase III trials in patients previously on diet/exercise alone, oral hypoglycemics, or insulin. It is unclear from the abstract, which parent trials the extension was based on.[14]

- Skyler et al. presents efficacy at 4-years (from the 3-month parent trials in type 1 or 2 diabetes) in patients who elected to continue inhaled insulin. Among the 204 patients enrolled in the extension, 89 completed 4-years.[15]

- Study 1022 is a 2-year outpatient, open-label non-inferiority trial comparing INH to SQ insulin in patients with type 1 diabetes. Change in HbA1c from baseline was the secondary endpoint. The primary endpoint was to evaluate pulmonary safety.[31]

- Study 1029 is a 2-year outpatient, open-label non-inferiority trial comparing INH to SQ insulin in patients with type 2 diabetes. Change in HbA1c from baseline was the secondary endpoint. The primary endpoint was to evaluate pulmonary safety.[32]

Table 3: Change in HbA1c from long-term trials

	n	Diabetes	Duration of study	Change in HbA1c from baseline	Dose of inhaled insulin
Rosenstock[12]					
• Inhaled to inhaled	44	type 1 and 2	1-year	-0.78 ± 0.87	Not given
• Inhaled to SQ	6			-0.72 ± 0.71	
• SQ to SQ	13			-1.06 ± 1.09	
• SQ to inhaled	39			-0.37 ± 0.75	
Barnett[13]					
• Inhaled + SU or metformin	336	type 2	1-year	-2.0*	10.1mg (week 4)
• SU + metformin	291			-1.8*	14.9mg (week 52)
Dreyer[34]					
• Inhaled + SU or metformin	158	type 2	2-year	-1.8*	13.8mg (week 24)
• SU + metformin	146			-1.5*	16.8mg (week 104)
Cefalu[14]					
INH	384	type 2	2-year	-1.5	not given
Study 1022[31]					
• INH	288	type 1	2-year	0.10	not given
• SQ	286			-0.18	
Study 1029[32]					
• INH	319	type 2	2-year	-0.4	not given
• SQ	316			-0.5	
Skyler[15]					0.15mg/kg (baseline)
Inhaled insulin	89	type 1 and 2	4-years	-0.48	0.18mg/kg (4 year)

*Additional concomitant diabetes therapies were allowed during the extension period

Patient satisfaction

Results of patient satisfaction studies should be interpreted with caution due to the open-label nature of the clinical trials. Patient satisfaction was evaluated in the 12-week trials by Cefalu et al and Skyler et al.[16, 17] A questionnaire comprised of 15 questions was administered to patients at baseline and at week 12. The 15 questions could be grouped into 2 domains: convenience/ease of use or social comfort. The response to each question was based on a 5-point Lickert scale ranging from "strongly agree" to "strongly disagree". The possible overall score ranges from 1-75, with a higher score indicating greater satisfaction. The development of the questionnaire was supported by Pfizer. The mean improvement in the satisfaction score was greater with inhaled insulin. Overall satisfaction scores and scores broken down by domain were also higher in the groups receiving inhaled insulin. Satisfaction persisted at 1-year.[12]

Table 4: Percent improvement in patient satisfaction

	Overall satisfaction		Convenience/ease of use domain		Social comfort domain	
	INH + ultralente	Regular/NPH	INH + ultralente	Regular/NPH	INH + ultralente	Regular/NPH
Gerber[16] Type 1 DM 12-weeks	35.1%*	10.6%	41.3%*	11.2%	28%	18%
Cappelleri[17] Type 2 DM 12-weeks	31%*	13%	-	-	-	-

Rosentstock[12] Type 1 and 2 1-year	37.9%*	3.1%	43.2%*	-0.9%	39.3%*	8.7%

*significant versus regular/NPH

Patient satisfaction was also evaluated in 2 of the 24-week trials by Quattrin et al. and Hollander et al.[18, 19] The satisfaction scale used in these trials were comprised of 12 subscales: advocacy, burden, convenience, efficacy, flexibility, general satisfaction, hassle, life interference, pain, preference, side effects, and social. The overall satisfaction score was scaled from 0-100. In type 2 diabetes, the overall satisfaction score increased with inhaled insulin and slightly decreased with SQ insulin (estimated treatment difference 17.5 points). In type 1 diabetes, the difference in satisfaction score between inhaled and SQ was 17.8 ± 1.0.

Changes in lipid parameters

Several trials of 12-24 weeks duration evaluated changes in lipid parameters.[5, 6, 8-11, 33] In the 12-week trials, triglycerides were lower in treatment regimens that included inhaled insulin compared to oral agents only.[8-10] In DeFronzo et al., there was a greater increase in LDL-C with rosiglitazone compared to inhaled insulin.[9] There were no clinically meaningful changes in any lipid parameter between inhaled insulin and SQ insulin in the 24-week trials.[5, 6, 11]

Table 5a: Changes in lipid parameters in INH + OHA trials

	Weiss (12-weeks)[8]	Rosenstock (12-weeks)[10]		Barnett (24-weeks)[33]	DeFronzo (12-weeks)[9]	
	Adjusted mean change				Median change	
	(INH + OHA) – OHA	(INH + OHA) - OHA	INH - OHA	(INH +SU) – (metformin + SU)	INH	Rosiglitazone
TC (mg/dl)	-2.13 [-13.96, 9.69]	-5 [-12, 1]	-3 [-10, 3]	0.17 [0.03, 0.31]	-2.0	10.5
HDL-C (mg/dl)	3.08 [-0.28, 6.44]	1 [-1, 3]	4 [1, 6]	0.0 [-0.04, 0.04]	4.0	3.0
LDL-C (mg/dl)	4.13 [-6.09, 14.36]	3 [-4, 10]	4 [-3, 10]	0.15 [0.02, 0.27]	4.5	15
TG (mg/dl)	-91.42 [-166.4, -16.4]	-54 [-76, -33]	-69 [-91, -48]	-0.04 [-0.2, 0.12]	-35	0

Table 5b: Median changes in lipid parameters in insulin only trials

	Hollander (type 2 DM)[11]		Quattrin (type 1 DM)[5]		Skyler (type 1 DM)[6]	
	Inhaled insulin	SQ insulin	Inhaled insulin	SQ insulin	Inhaled insulin	SQ insulin
TC (mg/dl)	0	3.0	1.0	-5.0	-4.0	5.0
HDL-C (mg/dl)	0	1.0	-1.5	1.0	-4.5	1.0
LDL-C (mg/dl)	-3.0	0	1.0	-6.5	-1.5	3.0
TG (mg/dl)	3.5	8.0	12	1.0	6.0	6.0

Studies were 24-weeks in duration

SAFETY

Inhaled insulin has been evaluated in approximately 2500 patients with type 1 or 2 diabetes. Approximately 2000 were exposed for more than 6 months and 800 for more than 2 years.[30]

The incidence of cough was greater in patients receiving inhaled insulin versus the comparator. In the type 1 diabetes studies, cough was reported in 25-27% of patients receiving inhaled insulin compared to 5-7% receiving SQ insulin.[4, 5] In the type 2 diabetes studies, the incidence of cough ranged from 8-21% with inhaled insulin compared to 1.5-2.0% in the comparator groups.[9-11] Cough was characterized as mild-moderate in nature with the incidence/prevalence decreasing over time. One study reported that the median duration of cough was 2 weeks.[11] Discontinuation of INH due to cough occurred in 1.2% of patients.[30]

Chest pain (not of cardiac origin) occurred in 4.7% of inhaled insulin groups and in 3.2% of comparator groups. Over 90% of these events were considered to be mild or moderate; 2 patients in the inhaled insulin group and 1 in the comparator group discontinued treatment because of chest pain.

Dry-mouth was reported in 2.4% and 0.8% of the inhaled insulin and comparator groups respectively. Over 98% of cases were mild-moderate in nature and no patient discontinued treatment for this reason.

Table 7: All-cause respiratory events in > 1% of any treatment group from Phase 2 and 3 trials

	Type 1 DM		Type 2 DM		
	INH (n=698)	SQ (n=705)	INH (n=1279)	SQ (n=488)	OHAs (n=644)
Respiratory tract infection	43.3	42	29.2	38.1	19.7
Increased cough	29.5	8.8	21.9	10.2	3.7
Pharyngitis	18.2	16.6	9.5	9.6	5.9
Rhinitis	14.5	10.9	8.8	10.5	3.0
Sinusitis	10.3	7.4	5.4	10	2.3
Respiratory disorder	7.4	4.1	6.1	10.2	1.7
Dyspnea	4.4	0.9	3.6	2.5	1.4
Sputum increased	3.9	1.3	2.8	1.0	0.5
Bronchitis	3.2	4.1	5.4	3.9	4.0
Asthma	1.3	1.3	2.0	2.3	0.5
Epistaxis	1.3	0.4	1.2	0.4	0.8
Laryngitis	1.1	0.4	0.5	0.4	0.3
Pneumonia	0.9	1.1	0.9	1.6	0.6
Voice alteration	0.1	0.1	1.3	0	0.3

Data from product package insert

Hypoglycemia

Hypoglycemia was defined as the following: characteristic symptoms and blood glucose measurement of <60mg/dl or blood glucose measurement < 50mg/dl regardless of whether characteristic symptoms were present, or characteristic symptoms without a blood glucose measurement that resolved with food, glucagons or IV glucose. Severe hypoglycemia was defined as patient unable to treat themselves, neurological symptoms and blood glucose < 50mg/dl or neurological symptoms without a blood glucose measurement that resolved with oral carbohydrate, SQ glucagon, or IV glucose.

The rate of all hypoglycemia was slightly lower with INH compared to regular insulin in type 1 diabetes. The rate of severe hypoglycemia was similar in the 12-week trial; however, in the 24-week trials, the rate was higher with inhaled insulin.

In type 2 diabetes, the rate of all hypoglycemia was higher with INH used either combination with OHAs or alone compared to OHAs alone, except in the 2-year extension study by Dreyer. In the study comparing the combination of INH or regular insulin with NPH, the rate of all hypoglycemia was slightly slower in the INH group; however, the rate of severe hypoglycemia was slightly higher.

Table 8: Hypoglycemic events

				All hypoglycemia (events/pt-month)		Severe hypoglycemia	
	Diabetes	Duration	Treatment arms	INH	Comparator	INH	Comparator
Skyler[4]	Type 1	12-weeks	INH + ultralente vs. regular + NPH	5.5	5.3	0.08	0.1
Quattrin[5]	Type 1	24-weeks	INH + ultralente vs. regular + NPH	8.6	9.0	5.5^	4.7^
Skyler[6]	Type 1	24-weeks	INH + NPH vs. regular + NPH	9.3	9.9	6.5^	3.3^
Weiss[8]	Type 2	12-weeks	INH + OHA vs. OHA	0.64	0.06	-	-
DeFronzo[9]	Type 2	12-weeks	INH vs. rosiglitazone	0.7	0.05	-	-
Rosenstock[10]	Type 2	12-weeks	INH + OHA vs. INH vs. OHA	1.7 1.3	0.1	-	-
Hollander [11]	Type 2	24-weeks	INH + ultralente vs. regular + NPH	1.4	1.57	0.5^	0.1^
Barnett [33]	Type 2	24-weeks	SU + INH vs. SU+ metformin	0.31	0.17		
Study 1002[30]	Type 2	24-weeks	Metformin + INH vs. metformin + SU	0.2 (L) 0.2(H)	0.2 (L) 0.1(H)		
Dreyer [34]	Type 2	2-years	SU/metformin + INH vs. metformin + SU	INH/OHA risk ratio= 0.81 [0.71, 0.92]			
Skyler[15]	Type 1 or 2	4-years		1.5	-	-	-

^Results are shown as events/100pt-month
H = high stratum (baseline HbA1c >9.5 - ≤ 12.5%); L = low stratum (baseline HbA1c ≥8% - ≤ 9.5%)
Per-protocol analysis used in Type 1 DM trials and ITT analysis used in Type 2 DM trials

Pulmonary function (Appendix 3)

Like other organs, the lung too may be a target for complications resulting from diabetes. Studies evaluating pulmonary microangiopathy and pulmonary mechanical function have been conducted in patients with diabetes. A recent study has shown that the decline in FEV1in patients with type 2 diabetes is 71ml/year compared to 25-30ml/year in healthy non-smokers. They found that the only predictor of reduced lung function was the level of glycemic control. Others have found an association between reduced lung function and other end-organ damage. Some studies have shown that diffusing capacity is reduced in patients with type 1 or 2 diabetes whose glycemia is poorly controlled. However, diffusing capacity in well-controlled patients with near normo-glycemia is nearly similar to non-diabetics.[25-27]

Pulmonary function tests were assessed in several of the clinical trials.[4-6, 8-15, 33] The majority of the studies showed a greater decrease in FEV1, and DLco for those groups receiving inhaled insulin. (See Appendix 3). These findings have lead to a more formalized study of lung function using highly standardized PFT monitoring. In a 2-year open-label trial in type 1 diabetes (Study 1022)[31] and type 2 diabetes (Study 1029),[32] pulmonary function (primary outcome) was evaluated in patients randomized to INH or SQ insulin (table 9). These studies are to continue to obtain data over 5 continuous years and 7 cumulative years of INH exposure.

Table 9: Change in pulmonary function tests at 2-years

	FEV1		DLco (mL/min/mmHg)	
	3-months	**2-years**	**3-months**	**2-years**
Type 1 diabetes (study 1022)[31]	-21mL [90%CI -41, -2mL]	-23mL [90%CI -44, 2mL]	-0.687 90%CI -0.969, -0.406]	-0.439 [90%CI -0.732, -0.145]
Type 2 diabetes (study 1029)[32]	-43mL [90%CI -65, -20mL]	-23mL [90%CI -47, -2mL]	-0.194 [90%CI -0.437, 0.050]	0.165 [90%CI -0.102, 0.432]

Change in FEV1 and DLco occur within the first several weeks of starting INH and do not progress over a 2-year treatment period. In patients with type 2 diabetes who were in the 2-year extension trial, it was shown that the treatment group difference in FEV1 resolved 6-weeks after discontinuing therapy with INH. Studies evaluating pulmonary function after discontinuing INH have not been conducted in patients with type 1 diabetes.[30, 34]

A decline in FEV1 of ≥ 20% from baseline was seen in 1.5% and 1.3% of INH and comparator groups respectively. A decline in DL_{CO} of ≥ 20% from baseline was seen in 5.1% and 3.6% of INH and comparator groups respectively.[30]

It is unknown at this time what the effect of using inhaled insulin is on lung function in patients with asthma or COPD. There are 2 ongoing studies in patients with asthma (Study 1028) and COPD (Study 1030). Preliminary data from these trials showed that the rate of non-severe pulmonary exacerbations was increased compared to the comparator groups.[36]

Weight gain

There was less weight gain with INH + basal insulin compared to regular + NPH insulin in patients with type 1 diabetes. This was also true in patients with type 2 diabetes receiving insulin only regimens. When INH was added to oral agents, weight increased with means ranging from 2.0-3.6kg. When INH was used as monotherapy the mean increase in weight ranged from 1.9-2.8kg.

Table 10: Weight gain

	Diabetes	**Duration**	**Treatment arms**	**Inhaled insulin**	**Comparator**
Skyler[4]	type 1	12-weeks	INH + ultralente vs. regular + NPH	+0.3kg	+0.7kg
Quattrin[5]	type 1	26-weeks	INH + ultralente vs. regular + NPH	+0.9kg	+1.5kg
Skyler[6]	type 1	24-weeks	INH + NPH vs. regular + NPH	+1.3kg	+1.5kg
Weiss[8]	type 2	12-weeks	INH + OHA vs. OHA	+2.7kg	+0.5kg

Hollander[11]	type 2	24-weeks	INH + ultralente vs. regular + NPH	Adjusted difference -1.29 kg [95% CI -1.98 to -0.59]	
DeFronzo[9]	type 2	3-months	INH vs. rosiglitazone	+1.9kg	+0.8kg
Rosenstock[10]	type 2	3-months	INH + OHA vs. INH vs. OHA	2.7kg (INH+OHA) 2.8kg (INH)	0
Barnett[33]	type 2	24-weeks	INH + SU vs. metformin + SU	+3.6kg (H) +2.4kg (L)	0 (H) -0.3kg (L)
Study 1002[30]	type 2	24-weeks	INH + metformin vs. SU + metformin	+2.8kg (H) +2.0kg (L)	+2.5kg (H) +1.6kg (L)

H = high stratum (baseline HbA1c >9.5 - ≤ 12.5%)
L = low stratum (baseline HbA1c ≥8% - ≤ 9.5%)

Insulin antibodies

Insulin antibody binding was reported in several studies.[5, 6, 9-11] Pooled data from these studies and 2 unpublished studies were evaluated for percent insulin antibody binding and whether there was an association with glycemic control, insulin dose, pulmonary function, or allergy/hypersensitivity.[20] Results were divided into patients with type 1 diabetes, type 2 diabetes previously using SQ insulin, and type 2 diabetes and not using SQ insulin. The greatest increase in median % insulin antibody binding was in patients with type 1 diabetes receiving inhaled insulin. There was no significant change in those who continued to receive SQ insulin. In the type 2 diabetes group previously on insulin, there was a slight increase in median % insulin antibody binding when given inhaled insulin. There was no change in the type 2 diabetes group (not on prior insulin) when given inhaled insulin.

Table 11: Percent insulin antibody binding

	Type 1 diabetes		**Type 2 diabetes prior insulin**		**Type 2 diabetes (no prior insulin)**	
	INH	**SQ**	**INH**	**SQ**	**INH**	**OHA**
Median % insulin antibody binding						
• Baseline	3%	4%	<3%	<3%	<3%	<3%
• End of study	29%	No sig change	6%	unchanged	unchanged	unchanged
Median % insulin antibody binding Difference [95%CI]	22% [19.5, 24.5]		3.5% [1.5, 4.5]		-	
Mean % insulin antibody binding	31% ± 20.3	-	13.1% ± 18.2	-	6.1% ± 8.7	-

There was no correlation between insulin antibody binding and HbA1c, FEV1, or DLco. Additionally there was no correlation between antibody level and HbA1c, hypoglycemia, FEV1, and DLco.

In 24-month extension trials where all patients received inhaled insulin, median antibody % binding ranged from 27-32% in type 1 diabetes patients, from 6-7% in type 2 patients on prior SQ insulin, and 3-5% in type 2 patients not on prior insulin.

All-cause allergic adverse events were slightly lower in patients receiving inhaled insulin compared to SQ insulin, except for skin and appendages (7% vs. 4.7% for INH and SQ respectively).

This issue was further prospectively studied in 40 type 1 diabetes patients who were randomized to receive NPH insulin twice daily and either SQ regular insulin or inhaled insulin for 24 weeks. Mean insulin antibodies increased from a baseline value of 3.5 ± 3.9 to 101.4 ± 140.4 µU/ml (median value 54 µU/ml) with inhaled insulin and remained stable in the SQ group. Blood glucose profiles, assessed by euglycemic glucose clamp studies following a standardized meal, were similar between the 2 groups.[21]

The increased binding seen with inhaled insulin does not appear to be associated with clinical response or adverse events; however, long-term data are needed.

CONTRAINDICATIONS

- Patients who smoke or who have recently quit smoking within the last 6 months of starting inhaled insulin. If smoking is resumed, inhaled insulin must be discontinued immediately, due to the increased risk of hypoglycemia.

- Patients with unstable or poorly controlled lung disease

PRECAUTIONS (pulmonary function, underlying lung disease)

- Inhaled insulin is not recommended in patients with underlying lung disease such as asthma or COPD.

- Baseline tests for lung function are recommended before beginning treatment and are recommended to be repeated after the first 6 months then annually thereafter. In patients that have a ≥ 20% decline in FEV1 from baseline, pulmonary functions tests should be repeated. If a ≥ 20% decline in FEV1 is confirmed, inhaled insulin should be discontinued. For patients with lesser declines in FEV1, more frequent monitoring may be required and discontinuation of inhaled insulin considered.

LOOK-ALIKE/SOUND-ALIKE DRUGS

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:
Inhaled insulin: Intal inhaler
Exubera: exenatide

In the literature, inhaled insulin is often abbreviated as INH. This is the same abbreviation used for isoniazid. Prescribers should write-out inhaled insulin and avoid using the abbreviation.

DRUG INTERACTIONS

Other inhaled agents

The pharmacokinetics of INH +/- albuterol or fluticasone was evaluated in non-diabetic subjects with mild-moderate asthma in a randomized open-label crossover study.[35] INH 3mg was administered alone versus albuterol 180mg followed by 3mg INH 30-minutes later versus fluticasone 440mcg followed by 3mg INH 30minutes later.

Premedication with albuterol increased the insulin AUC_{0-6h} by 24% and 51% in the mild and moderate asthmatics respectively. Insulin Cmax was increased by 35% and 47% respectively. Prior administration of fluticasone had no significant effect on INH kinetics (data not shown).

Table 12: Effect of albuterol on inhaled insulin kinetics in mild-moderate asthma

	Mild asthma (FEV1 80-100% predicted)		Moderate asthma (FEV1 50-79% predicted)	
	Albuterol + INH	**INH**	**Albuterol + INH**	**INH**
Insulin AUC_{0-6h}	2941	1953	5052	4056
Insulin Cmax	29.6	20.1	46.8	34.6

The manufacturer recommends that the administration of other inhaled agents relative to inhaled insulin be consistent. However, note that INH is not recommended for use in patients with asthma or COPD.

Smoking

Three studies, 2 using Exubera[22, 23] and the other using AERx®iDMS®[24], have evaluated the effect of smoking on the pharmacokinetics of single doses of inhaled insulin. Both studies showed that the insulin Cmax and AUC were higher and that Tmax was approximately 22minutes faster in smokers compared to nonsmokers.

Table 13: Effect of smoking on inhaled insulin kinetics

	AUC_{0-6}		Cmax		Tmax (min)	
	smoker	**nonsmoker**	**smoker**	**nonsmoker**	**smoker**	**nonsmoker**
Exubera[22]	4847µU·min/mL	1410 µU· min/mL	72 µU/ml	16 µU/ml	31	53
AERx®iDMS®[24]	40mU · l/h	13.940mU · l/h	42 mU/l	13.9 mU/l	31.5	53.9

The Exubera study also showed the effects that 13 weeks of smoking cessation had on inhaled insulin. The AUC and Cmax decreased to 3357µU·min/mL, 45 µU/ml respectively while Tmax slightly increased by 3minutes.[22] In another study, these same investigators found that smoking resumption reversed the effects of smoking cessation.[23]

The effect of passive smoke on the pharmacokinetics of inhaled insulin was evaluated in 30 healthy non-smoking volunteers. Inhaled insulin was administered after subjects were exposed to 2-hours of passive cigarette smoke. The insulin AUC and Cmax were reduced by approximately 20% and 30% respectively. The pharmacokinetics of inhaled insulin in non-smokers has not been studied in the setting of chronic exposure to passive cigarette smoke.[30]

HOW SUPPLIED

Inhaled insulin is packaged in single-dose blister packs containing 1mg or 3mg of insulin and is to be administered via the Nektar Pulmonary Inhaler.

The inhaler consists of the inhaler base, a chamber, and an Exubera Release Unit
The inhaler may be used for up to 1 year from the date of first use.
The Exubera Release Unit in the inhaler should be changed every 2 weeks

The Exubera kit contains the inhaler, chamber, 2 release units, and blisters of 1mg and 3mg of insulin. The combination packs contain 2 release units and 1mg and 3mg blisters of insulin. The inhaler and inhaler components can be purchased separately. At present, Exubera is only available as a combination pack containing 1mg and 3mg blisters. Individual packs containing only 1mg or 3mg are not available at this time; however, may be available in the future.

Exubera Inhalation Powder		**Exubera Inhaler and components**	
Exubera kit	1 inhaler 1 replacement chamber 1mg x 180 blisters 3mg x 90 blisters 2 release units	Exubera Inhaler & chamber	1 inhaler 1 replacement chamber
Exubera combination pack 12	1mg x 90 blisters 3mg x 90 blisters 2 release units	Exubera Release Units	2 Release Units
Exubera combination pack 15	1mg x 180 blisters 3mg x 90 blisters 2 release units	Exubera Chamber	1 replacement chamber

DOSAGE AND ADMINISTRATION

- 1mg blister of inhaled insulin is approximately equal to 3 units of subcutaneous regular human insulin
- 3mg blister of inhaled insulin is approximately equal to 8 units of subcutaneous regular human insulin
- Insert unit dose blister into inhaler. Pump handle of inhaler, press button to pierce blister. Insulin powder is dispersed into chamber and ready for inhalation
- Administer no more than 10 minutes prior to meals
- Patients with type 1 diabetes will still require injectable basal insulin
- Three 1mg doses should not be substituted for one 3mg dose. It was found that Cmax and AUC of three 1mg blisters were approximately 30% and 40% higher respectively compared to one 3mg blister.
- Up to 45% and 25% of the contents may be retained in the blister for the 1mg and 3mg blisters respectively
- If the 3mg blisters become temporarily unavailable for a patients stabilized on a regimen that included the 3mg blisters, two 1mg blisters may be substituted for one 3mg blister

Because INH is dosed in milligrams and subcutaneous injected as units, there is a potential risk of dosing errors as patients and providers may confuse units and milligrams.

There is a potential risk for error as 3 x 1mg blisters are not equivalent to 1x 3mg blister

The inhaled insulin device and drug packaging may limit sufficiently fine adjustment of insulin dose.

Initial dosing may be based on weight using the guidelines in table 12. Additional factors that should be taken into consideration when determining a starting dose include patient's current glycemic control,

previous response to insulin, dietary and exercise habits. Further dose adjustment should be based on results of blood glucose monitoring.

Table 14: Initial dosing recommendations

Patient weight	Initial dose per meal	# of 1mg blisters per dose	# of 3mg blisters per dose
30 - 39.9kg	1mg per meal	1	-
40 – 59.9 kg	2mg per meal	2	-
60 – 79.9 kg	3 mg per meal	-	1
80 – 99.9 kg	4 mg per meal	1	1
100 – 119.9kg	5 mg per meal	2	1
120-139.9 kg	6mg per meal	-	2

Inhaled insulin may be used during intercurrent respiratory infections (e.g. bronchitis, upper respiratory tract infection, and rhinitis). Blood glucose levels should be closely monitored.[30] There is no experience using inhaled insulin in patients with pneumonia.[36]

Storage
Unopened blister packs should be stored at room temperature. Excursions between 59-86°F are permitted. Do not refrigerate or freeze.

Once the foil overwrap is opened, unit dose blisters should be protected from moisture and stored at room temperature. Excursions between 59-86°F are permitted. Do not refrigerate or freeze. Unit dose blisters should be used within 3 months of opening foil overwrap. Return blisters to overwrap to protect from moisture.

COST
Initial dosing is based on the formula that pre-meal dose = weight (kg) x 0.05mg/kg. Using an average weight of 85kg in a patient with type 2 diabetes, this would amount to 4mg of INH before each meal (assuming 3 meals/day). This dose would be best achieved using the combination 12 pack at a cost of $2.79/day. This does not include the initial cost of the inhaler and replacement chamber.

Table 15a: VA Acquisition Cost

Exubera kit (1 inhaler, 1 replacement chamber, 1mg x 180 blisters, 3mg x 90 blisters, 2 release units)	$112.28
Exubera combination pack 12 (1mg x 90 blisters, 3mg x 90 blisters, 2 release units)	$83.84
Exubera combination pack 15 (1mg x 180 blisters, 3mg x 90 blisters, 2 release units)	$104.79
Exubera Inhaler & chamber	$67.96
Exubera Release Units (2 pack)	$3.72
Exubera Chamber	$11.17

Cost of other drugs that may be added to patients who have not achieved glycemic control with 2 oral agents.

Table 15b

Drug	Qty/month	Cost/month
Regular insulin 10mL vial	1-2 vials/month	$6.95 - 13.90
Insulin aspart 10mL vial	1-2 vials/month	$24-48
NPH insulin 10mL vial	1-2 vials/month	$6.85-13.70
Insulin glargine 10mL vial	1-2 vials/month	$27.96-55.92
Rosiglitazone	4-8mg once daily	$47.70-77.10
Exenatide	5-10mg BID	$107.21-128.05

Does not include price of needles, syringes, blood glucose monitoring supplies, etc.
Price of insulin pens and cartridges are higher than the price of 10mL vials

PHARMACOECONOMICS

The National Institute for Health and Clinical Excellence (NICE) conducted a cost-utility analysis using a validated model (EAGLE) submitted by the manufacturer. Based on assumptions used by NICE, the group concluded that Exubera was not cost effective. These results contrast with those obtained by the manufacturer because of different assumptions used. http://www.nice.org.uk/page.aspx?o=207029

A pharmacoeconomics model that allows the user to input variables specific to one's patient population is available by the manufacturer. This model utilizes data from the studies by Hollander, DeFronzo, and Rosenstock.[9-11] Data from UKPDS were used to estimate the incidence of mortality, stroke, MI, etc.

POSTMARKETING STUDY COMMITMENTS

The manufacturer has agreed to the following post-marketing study commitments requested by the FDA.

Table 16: Post-marketing clinical trial commitments

Study	Outcomes to be evaluated	Study start/finish dates
Study 1069 - Real world trial of Exubera vs. usual care in 5000 patients Type 1 or Type 2 diabetes	1. Estimate the relative risk of > 20% decline in lung function using pulmonary function tests 2. Clinical risk associated with increased insulin antibody formation and relative risk of developing allergic and immune disorders	Start date: July 2006 Final report submission: Dec. 2015
Completion of study 1022 Type 1 diabetes	Changes in lung function over 5 continuous years and 7 cumulative years of Exubera exposure	Study in progress Final report submission: Dec. 2013
Completion of study 1029 Type 2 diabetes	Changes in lung function over 5 continuous years and 7 cumulative years of Exubera exposure	Study in progress Final report submission: Dec. 2013
Completion of study 1028 Diabetics with mild-moderate asthma	1. Assess change in FEV1 and DLco 2. Diabetes control and asthma 3. Frequency and severity of asthma exacerbations	Study in progress Final report submission: Dec. 2008
Completion of study 1030 Diabetics with COPD	1. Assess change in FEV1 and DLco 2. Diabetes control and underlying COPD 3. Frequency and severity of COPD exacerbations	Study in progress Final report submission: Dec. 2012
	Assess adequacy of the Package Insert for prescribers and Medication Guide for patients in preventing use of Exubera by smokers	Start date: August 31, 2006 Annual interim reports Final report submission: Dec. 2011

CONCLUSIONS

In patients with type 1 diabetes or type 2 diabetes using insulin only, inhaled insulin was found to be non-inferior to injectable regular insulin. Addition of inhaled insulin to oral agents further reduces HbA1c (mean reduction ranging from -1.8 to 2.2%). In type 2 diabetes, monotherapy with inhaled insulin reduced HbA1c by a mean of 2.2% in treatment naïve patients and by 1.4% in those on prior OHAs.

The overall rate of hypoglycemia was higher with combination INH + OHA or monotherapy INH compared to OHA alone. In type 1 or type 2 patients using only insulin, the overall rate of hypoglycemia was slightly lower with INH compared to regular insulin; however, the rate of severe hypoglycemia was slightly higher with INH. Long-term consequences on pulmonary function beyond 2 years are unknown.

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Prepared by Deborah Khachikian, PharmD
July 2006

Appendix 1: Published clinical trials in Type 1 diabetes (see page 23 for list of abbreviations used)

Trial	Inclusion/exclusion	Treatment regimen	Baseline information	Results
Skyler 2001[4] **Phase II trial** R, OL, PR USA Duration: 3-months **INH (n) / SQ (n)** R 35 / 37 ITT 35 / 36 Non-inferiority design ITT- population	Type 1 DM 18-55 years old 80-130% of ideal weight Stable insulin regimen of ≥ 2 injections daily for ≥ 2 months HbA1c 7-11.9% C-peptide ≤ 0.2nmol/l Normal CXR, PFTs, EKG Willingness to perform SMBG 4 times daily Non smoker for ≥ 6 months **Exclusions:** asthma or other respiratory diseases, cardiac, cerebrovascular, liver disease, or renal insufficiency, significant h/o allergy or atopy, seizures, diabetic autonomic neuropathy (gastroparesis, orthostasis), ≥2 serious hypoglycemic episodes in previous year, hospital or ER admission with poor diabetes control in previous 6 months, insulin pump, ≥ 4 daily doses of insulin or 150units daily, systemic steroid use, pregnacy	During 4-week lead-in, patients continued usual pre-study regimen Randomization stratified according to HbA1c ≤ 8.5% and > 8.5% INH before meals (1-2 inhalations of 1or 3mg) + single bedtime ultralente insulin vs. Patients usual regimen given 2-3 times daily (NPH before breakfast and bedtime/regular insulin before 2-3 meals) Both groups had weekly adjustments to achieve preprandial target of 100-160mg/dl SMBG performed 4 times daily. Weekly adjustments made from previous weeks SMBG results to achieve pre-meal glucose of 100-160mg/dl Patients were allowed to adjust insulin dose when preprandial glucose was outside the range or in anticipation of a smaller or larger meal than usual	**Values for inhaled insulin+ ultralente / regular + NPH insulin** **% male:** 56% / 53% **% white:** 83% / 78% **Age (years):** 35.4 ± 9 / 39.7 ± 8.6 **Duration of DM (years):** 14.6 ± 9.3 / 14.4 ± 9.3 **HbA1c (%):** 8.5 ± 1.1 / 8.5 ± 1.1 **Weight males (kg):** 81.1 ± 11.3/ 82.2 ± 10.8 **Weight females (kg):** 64.6 ± 7 /64.8 ± 8.6 **BMI males (kg/m^2):** 25.1 ± 2.7 / 26 ± 2.5 **BMI females (kg/m^2):** 24.4 ± 2.3 / 24.6 ± 3.3 **Regular insulin dose (units):** 17.9 / 15.7 **Long-acting insulin dose (units):** 29.9 / 30.8 Mean ± SD	**INH + ultralente / Regular+ NPH** Dropouts (n): 0/35 / 1/37 HbA1c (%): -0.64 / -0.83 End HbA1c (%): 7.9 ± 1 / 7.7 ± 0.9 HbA1c % (adjusted treatment difference): 0.2% [95%CI -0.2 to 0.5] Weight (all patients): +0.3kg / +0.7kg % hypoglycemia Mild-moderate/severe: 94.3% / 14.3% / 83.8% / 13.5% Hypoglycemia (events/ pt-month): 5.5 / 5.3 Severe hypoglycemia (events/ pt-month): 0.08 / 0.10 Insulin dose (bolus/basal): 36.6 ± 14.7^ 24.8 ± 9.3 / 15.9 ± 9.8 31 ± 13.2 ^dose converted from mg to units mean values
Quattrin 2004[5] **Phase III trial** R, OL, PR USA, Canada Duration: 24 weeks **INH (n) / SQ (n)** R 170 / 165	Type 1 DM ≥ 1 year 12-65 y/o Stable insulin regimen of ≥ 2 injections daily for ≥ 2 months prior to study BMI ≤ 30kg/m^2 C-peptide ≥ 0.2pmol/ml HbA1c 6-11% **Exclusions:** poorly controlled	During 4-week lead-in, all patients received NPH+ regular before breakfast, regular before dinner, and 2nd NPH dose before dinner or at bedtime INH before meals (1-3 inhalations of 1or 3mg within 10 minutes) + single bedtime	**Values for inhaled insulin + ultralente / regular + NPH insulin** **% male**: 51.8% / 55.5% **Age (years):** 33 (11-63) / 34 (11-64) **Duration of DM (years):** 16.2 (1-41) / 16.5 (1-49) **HbA1c (%):** 8.1± 1.0 / 8.1 ± 1.0 **FPG (mg/dl):** 194 / 203 **Weight males (kg):** 82 (49-131) /	**INH + ultralente / Regular + NPH** Completed study (n): 152 / 151 HbA1c (%): -0.2 / -0.4 End HbA1c (%): 7.9 ± 1.1 / 7.7 ± 0.9 HbA1c (adjusted treatment difference): 0.16% [95%CI -0.01 to 0.32] % achieving HbA1c < 8%: 64%% / 68.2%% % achieving HbA1c < : 16.9% / 19.7%

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Non-inferiority design

Assessments made on per-protocol group (defined as no major inclusion/exclusion violation and received at least 12 weeks of treatment, had baseline and at least 1 post-tx HbA1c)
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asthma, significant COPD, other significant respiratory disease, smoked in the last 6 months, significant CXR abnormalities, DLco <75%, TLC < 80% or > 120%, FEV1 < 70% predicted, clinically significant major organ system disease (excluding DM microvascular complications), abnormal EKG or labs, use of systemic glucocorticoids, h/o of ≥ 2 severe episodes of hypoglycemia in last 6 mos., hospitalization or ER visit due to diabetes in last 6 mos., use of insulin past in last 2 mos., insulin dose > 150units/d, pregnancy
</td>
<td>
ultralente insulin
vs.
continue regimen of 2-3 regular/NPH injections daily

Initial inhaled dose based on wt., and known response to injected insulin. Ultralente dose based on glycemic control and previous NPH requirement

Inhaled and SQ dosing adjusted to achieve target pre-meal glucose of 80-140mg/dl and bedtime value of 100-160mg/dl
</td>
<td>
78.1 (38-110)
Weight females (kg): 65.4 (35-91) / 67.2 (40-93)
BMI males (kg/m^2): 25.7 (17-36) / 25 (18-32)
BMI females (kg/m^2): 24.7 (18-34) / 24.9 (18-33)
Short-acting insulin (units): 21 (2-64) / 21.28 (4-80)
Long/intermediate-acting insulin (units): 35.37 (6-94)/ 34.48 (5-116)

Mean (range)
</td>
<td>
7%
FPG (mg/dl) -35 -10
FPG (adjusted treatment difference) -25.17mg/dl [95%CI -43.39 to -6.95]
2h-PPG (adjusted treatment difference) -30.28mg/dl [95%CI -54.6 to -6.01]
Weight (kg) +0.9 +1.5
Hypoglycemia (events/ patient-month) 8.6 9.0
Severe hypoglycemia (events/100-pt-month) 5.5 4.7
Cough 27% 5%
Dose 14.2mg similar to baseline
</td>
</tr>
<tr>
<td>
Skyler 2005[6]
Phase III trial
R, OL, PR
USA and Canada
Duration: 24 weeks

<table>
<tr><th></th><th>INH (n)</th><th>SQ (n)</th></tr>
<tr><td>R</td><td>163</td><td>165</td></tr>
<tr><td>PP</td><td>159</td><td>159</td></tr>
</table>
Non-inferiority study design

Per-protocol population analysis defined as having received at least 12 out of 24 weeks of treatment and had postbaseline HbA1c
</td>
<td>
Type 1 DM ≥ 1 year duration
12-65 years old
Stable insulin regimen of ≥ 2 injections daily for ≥ 2 months prior to study
BMI ≤ 30kg/m^2
C-peptide ≤ 0.2pmol/ml
HbA1c 6-11%
willingness to perform SMBG

Exclusions: poorly controlled asthma, other significant respiratory, renal, or cardiac disease, smoked in the last 6 months, significant insulin allergy, recurrent severe hypoglycemia, systemic glucocorticoid use or insulin pump use in past 2 mos., insulin dose >150 units/day, hospitalization/ER visit due to poor DM control in past 6 mos., pregnancy
</td>
<td>
During the 4-week run-in, patients received premeal regular insulin and twice daily NPH

INH before meals (1-2 inhalations of 1or 3mg) + morning and bedtime NPH
vs.
Regular insulin before meals + morning and bedtime NPH

INH given within 10 minutes before meals

Initial inhaled dose based on wt. and known response of equivalent SQ doses

SMBG to be performed at least 5x/day (before meals, 2h post-prandial, and bedtime)

Target pre-meal glucose of 80-120mg/dl and bedtime value of 100-140mg/dl
</td>
<td>
Values for inhaled insulin+ NPH / Regular + NPH insulin
% male: 52.5%/ 54%
Age (years): 29.3 ± 14.5 / 29.7 ± 14.7
Duration of DM (years): 12.9 (1.0-50) / 14.6 (1.0-49)
HbA1c (%): 8.24 ± 1.08/ 8.2 ± 1.16
Weight (kg): 70.1 ± 14.9 / 70.8 ± 15.4
BMI (kg/m^2): 24.3 ± 3.4/ 24.4 ± 3.7
Short-acting insulin (units): 24/ 25.4
Long/intermediate-acting insulin (units): 35.2/ 34.5

Mean ± SD
Mean (range)
</td>
<td>
<table>
<tr><th></th><th>INH + NPH</th><th>Regular + NPH</th><th>CI for difference</th></tr>
<tr><td>Completed study (n)</td><td>154</td><td>152</td><td></td></tr>
<tr><td>HbA1c</td><td>-0.3</td><td>-0.1</td><td>-0.16 [-0.34, 0.01]</td></tr>
<tr><td>% achieving HbA1c < 8%</td><td>74.8%</td><td>66%</td><td>-</td></tr>
<tr><td>% achieving HbA1c < 7%</td><td>28.2%</td><td>30.1%</td><td>OR=1.53 [0.75, 3.14]</td></tr>
<tr><td>FPG (mg/dl)</td><td>-35</td><td>+4</td><td>-39.53[-57.5, -21.6]</td></tr>
<tr><td>2-h PPG (mg/dl)</td><td>-21</td><td>-14</td><td>-6.78 [-30.29, -16.74]</td></tr>
<tr><td>Weight (kg)</td><td>+1.3</td><td>+1.5</td><td>-0.19[-0.91, 0.53</td></tr>
<tr><td>Hypoglycemia (events/pt-month)</td><td>9.3</td><td>9.9</td><td>RR=0.94 [0.91, 0.97]</td></tr>
<tr><td>Severe hypoglycemia (events/100-pt-month)</td><td>6.5</td><td>3.3</td><td>RR=2.0 [1.28, 3.12]</td></tr>
<tr><td>Severe hypoglycemia (# episodes/ # pts.)</td><td>58/25</td><td>29/22</td><td></td></tr>
<tr><td>Cough</td><td>25%</td><td>7%</td><td>-</td></tr>
<tr><td>Dose (short/long-acting)</td><td>10.8mg/ 38.1 units</td><td>26.8 units/ 37.8 units</td><td></td></tr>
</table>
Mean values
</td>
</tr>
</table>

Appendix 2: Clinical trials in Type 2 diabetes (see page 23 for list of abbreviations used)

Trial	Inclusion/exclusion	Treatment regimen	Baseline information	Results
Cefalu 2001[7] **Phase II trial** R, OL USA N=26 Duration: 12 weeks Non-inferiority design	Type 2 DM HbA1c 7-11% 35-65 years old Stable insulin regimen of 2-3 injections daily for ≥ 1 month Weight 100-175% of ideal C- peptide ≥ 0.2pmol/mL Normal chest and pulmonary function **Exclusions:** SCr ≥ 3mg/dl, major organ disease (except HTN, peripheral neuropathy, mild nephropathy, retinopathy), smoked in the last 6 months, ≥ 4 daily doses of insulin or 150units daily, oral hypoglycemics, insulin pump	During 4-week lead-in, patients continued their usual insulin therapy INH before meals + single bedtime ultralente insulin Usual regimen of 2-3 regular/NPH injections daily The insulin dose was adjusted if mean preprandial glucose value since previous visit was outside 100-160mg/dl range	**% male:** 61.5% **BMI males (kg/m^2):** 30 (range 23-37) **BMI females (kg/m^2):** 33 (range 26-41) **Age (years):** 51.1 (range 39-64) **Duration of DM (years):** 11.2 (range 0.9-35) **HbA1c (%):** 8.67 ± 1.44 **Baseline insulin dose:** 19 units regular, 51 units long-acting	Data for the comparator group (SQ insulin) was not reported. INH was non-inferior to SQ insulin **Inhaled insulin:** HbA1c (%): -0.71 ± 0.72 [95% CI -1.00 to -0.42] There were 39 hypoglycemic events (weeks 1-4) and 22 event (last 8 weeks) Mild-moderate hypoglycemia (episodes/month): 0.83 Severe hypoglycemia : none Insulin dose (bolus/basal): 14.6 ± 5.1mg / 35.7 ± 18.4 units weight: -0.3 ± 2.9kg
Weiss 2003[8] **Phase II trial** R, OL, PR USA Duration: 12 weeks **INH+ OHA (n)** / **OHA (n)** R: 33 / 36 ITT: 32 / 36 Superiority study design ITT-LOCF analysis	Type 2 DM HbA1c 8.1- 11.9% despite tx with therapeutic dose of SU +/or metformin 35-65 year old C-peptide ≥ 0.2pmol/ml Weight 100-175% of ideal Normal CXR and PFTs **Exclusions:** major organ system disease, epilepsy, asthma or other respiratory diseases, ≥2 hypoglycemic episodes in previous year, smoking in the previous 6 months	During 4-week lead-in, patients continued their usual OHA INH before meals* + OHA vs. OHA only *Initial preprandial INH dose based on body weight: < 60kg = 2mg, 60-80kg = 3mg, 80-99kg =4mg INH given within 10 minutes before meals Dose of OHA was unchanged from baseline dose SMBG performed at least 4 times daily for INH group and twice daily for OHA only group. Insulin doses adjusted weekly based on SMBG to achieve pre-meal glucose of 100-160mg/dl If SMBG value outside the	**Values for inhaled insulin + OHA / OHA** **% male:** 57.6% / 72.2% **% white:** 70% / 58.3% **Age (years):** 52.7 ± 1.37 / 49.9 ± 1.37 **Duration of DM (years):** 9.5 (2-18) / 6.9 (1-19) **HbA1c (%):** 9.8 ± 0.2 / 9.9 ± 0.2 **FPG (mg/dl):** 227.48 ± 8.69 / 254.06 ± 11.54 **Weight (kg):** 92.3 ± 2.68 / 91.6 ± 2.02 **BMI males (kg/m^2):** 30.8 ± 0.7 / 29.9 ± 0.6 **BMI females (kg/m^2):** 32.1± 0.9 / 33.3 ± 0.9 **% using SU only:** 36.4/ 47.3 **% using metformin only**: 6.1%/ 2.8% **% using SU + metformin**: 57.5/ 47.2 Mean ± SD Mean (range)	

	INH+ OHA	OHA
Drop-outs	0	0
HbA1c (%)	7.5 ± 0.2	9.8 ± 0.2
HbA1c (adjusted treatment difference)	-2.2 [95%CI -2.7 to -1.7]*	
% achieving HbA1c < 8%	66%*	8%
% achieving HbA1c < 7%	34%	<7%
FPG (mg/dl)	-61.6 ± 1.25	-0.92 ± 0.27
FPG (adjusted treatment difference)	-60.7mg/dl [95%CI -80.6 to -40.73]*	
2-h PPG (mg/dl)	-25.6 ± 1.1	-9.18 ± 1.0
2-h PPG (adjusted treatment difference)	-16.22mg/dl [95%CI -33.56 to 0.76]	
PPG AUC_{0-2h} (adjusted treatment difference)	-173.75 [-226.86 to -120.62]*	
Weight (kg)	+2.7	+0.5
Weight (adjusted treatment difference)	2.5kg [95%CI 1.3 to 3.7]*	
Any hypoglycemia	69%	17%
Hypoglycemia (# episodes/ # pts.	57/22	6/6
Severe hypoglycemia (n)	1	0
Hypoglycemia (events/pt-	0.64	0.06

<table>
<tr>
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<td>range, patients adjusted insulin dose accordingly</td>
<td></td>
<td>
<table>
<tr><td>month)</td><td></td><td></td></tr>
<tr><td>Risk ratio for hypoglycemia INH+OHA/ OHA</td><td colspan="2">10.7 [95% CI 4.6 to 24.8]*</td></tr>
<tr><td>Daily INH dose (mg)</td><td>12.7 ± 1.0</td><td>NA</td></tr>
</table>
Mean ± SE
*significant vs. OHA
</td>
</tr>
<tr>
<td>Hollander 2004[11]
Phase III trial
R, OL, PR
USA, Canada
Duration: 6 months
<table>
<tr><th></th><th>INH (n)</th><th>SQ (n)</th></tr>
<tr><td>R</td><td>149</td><td>149</td></tr>
<tr><td>PP</td><td>143</td><td>145</td></tr>
</table>
Non-inferiority design

Assessments made on per-protocol group (defined as no major inclusion/exclusion violation and received at least 12 weeks of treatment, had baseline and at least 1 post-tx HbA1c)</td>
<td>Type 2 DM
35-80 years old
≥ 1 year
Stable insulin regimen of 2-3 insulin injections daily for ≥ 2 months
No oral hypoglycemics
BMI ≤ 35kg/m^2
C-peptide ≥0.2pmol/ml
HbA1c 6 -11%

Exclusions: poorly controlled asthma, COPD, other significant respiratory disease, smoked in the last 6 months, abnormal CXR, DL_{CO} <75%, TLC <80% or >120%, FEV1 < 70% pred.,systemic steroid use, ≥2 severe hypoglycemic episodes in past 6 mos., hospitalization/ER visit due to poor DM control in past 6 mos., insulin pump use in past 2 mos., insulin dose >150 units/day, other major disease, clinically significant abnormal labs</td>
<td>During 4-week lead-in, all patients received 2 doses of mixed regular /NPH

INH before meals (1-2 inhalations of 1or 3mg within 10 minutes) + single bedtime ultralente insulin
vs.
Continue current regimen of 2 doses of mixed regular/NPH injections daily

Initial inhaled dose based on wt., baseline SQ dose, and previous response to insulin.

SMBG to be performed before breakfast, lunch , dinner, and bedtime

Dose adjusted weekly by investigator to achieve target pre-meal glucose of 80-140mg/dl and bedtime value of 100-160mg/dl
Patients were allowed to adjust insulin dose when preprandial glucose was outside the range or in anticipation of a smaller or larger meal than usual</td>
<td><u>Values for inhaled insulin+ ultralente / Regular + NPH insulin</u>

% male: 66%
Age (years): 58.7 ± 9.5 / 56.2 ± 11.1
Duration of DM (years): 13.8 (0.4-59) / 13.2 (0.9-43.4)
HbA1c (%): 8.48 ± 1.24 / 8.47 ± 1.2
FPG (mg/dl): 152/ 158
Weight (kg): 89.9 ± 14.2 / 88.8 ± 13.7
BMI males (kg/m^2): 29.9 ± 3.8/ 29.5 ± 3.6
BMI females (kg/m^2): 31.7 ± 5.1 / 31.1 ± 3.9
Short-acting insulin (units): 23.17 (1-92) / 23.79 (4-110)
Long/intermediate-acting insulin (units): 41.27 (5-115) / 41.66 (8-144)
Premixed insulin (units): 61.79 (14-140) / 49.03 (11-90)

Mean ± SD
Mean (range)</td>
<td>
<table>
<tr><th></th><th>INH + ultralente</th><th>Regular + NPH</th></tr>
<tr><td>Completed study (n)</td><td>132</td><td>140</td></tr>
<tr><td>HbA1c (%)</td><td>-0.7</td><td>-0.6</td></tr>
<tr><td>HbA1c (adjusted diff vs. control)</td><td colspan="2">-0.07 [95% CI -0.32 to 0.17]</td></tr>
<tr><td>% achieving HbA1c < 8%</td><td>76.2%</td><td>69%</td></tr>
<tr><td>% achieving HbA1c < 7%</td><td>47%</td><td>32%</td></tr>
<tr><td>FPG (adjusted diff vs. control)</td><td colspan="2">-15.9mg/dl
[95% CI -26.6 to -5.2]</td></tr>
<tr><td>2-h PPG (adjusted diff vs. control)</td><td colspan="2">-9.41mg/dl
[95% CI -26.9 to 8.0]</td></tr>
<tr><td>Weight (adjusted diff vs. control)</td><td colspan="2">-1.29 kg
[95% CI -1.98 to -0.59]</td></tr>
<tr><td>daily insulin dose (bolus/basal)</td><td>16.6mg / 37.9units</td><td>25.5 units / 52.3 units</td></tr>
<tr><td>Hypoglycemia (%)</td><td>76.2%</td><td>71.7%</td></tr>
<tr><td>Hypoglycemia (events/ patient-month)</td><td>1.4</td><td>1.57</td></tr>
<tr><td>Hypoglycemia</td><td colspan="2">RR=0.89 [0.82 to 0.97]</td></tr>
<tr><td>Severe hypoglycemia (events/100-pt-month)</td><td>0.5</td><td>0.1</td></tr>
<tr><td>Deaths (n)</td><td>2</td><td>0</td></tr>
<tr><td>cough</td><td>21%</td><td>2%</td></tr>
</table>
</td>
</tr>
<tr>
<td>DeFronzo 2005[9]
Phase III trial
R, OL, PR
USA
Duration: 3-months
<table>
<tr><th></th><th>INH (n)</th><th>RSG (n)</th></tr>
<tr><td>R</td><td>76</td><td>69</td></tr>
</table>
</td>
<td>Type 2 DM ≥ 2 months
stable diet and exercise regimens for ≥ 2 months
no pharmacologic tx for DM
30-80 years old
HbA1c 8-11%
C-peptide ≥ 0.2pmol/ml
BMI ≤ 40kg/m^2
Willingness to perform</td>
<td>During the 4-week run-in, patients to maintain ADA diet exercise recommendations

INH prior to meals (1-2 inhalations of 1or 3mg)
vs.
Rosiglitazone 4mg BID</td>
<td><u>Values for inhaled insulin / rosiglitazone</u>
% male: 64%/ 46%
Age (years): 53 ± 10.7 / 54.4 ± 11
Duration of DM (years): 4.3(0.08-22) / 3.1 (0.01-18)
HbA1c (%): 9.5 ± 1.1/ 9.4 ± 0.9
BMI (kg/m^2): 31.9 ± 4.7/ 32.7 ± 6.6
FPG (mg/dl): 208 ± 56/ 199 ± 50</td>
<td>
<table>
<tr><th></th><th>INH only</th><th>Rosiglitazone</th><th>Adjusted difference [95%CI]</th></tr>
<tr><td>Completed study (n)</td><td>71</td><td>63</td><td></td></tr>
<tr><td>% achieving HbA1c < 8%</td><td>82.7%</td><td>58.2%</td><td>Adjusted odds ratio 7.14[2.48, 20.58]*</td></tr>
<tr><td>% achieving HbA1c < 7%</td><td>44%</td><td>17.9%</td><td>Adjusted odds ratio 4.43[1.94, 10.12]</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr>
<td>ITT 75 67

Superiority study design
ITT-LOCF analysis</td>
<td>SMBG

Exclusions: poorly controlled asthma, COPD, other significant respiratory disease, smoked in the last 6 months, abnormal CXR or EKG, DL_{CO} <75%, TLC <80% or >120%, FEV1 < 70% pred., use of systemic steroid or other drugs affecting glucose, ≥2 severe hypoglycemic episodes in past 6 mos., hospitalization/ER visit due to poor DM control in past 6 mos., pregnancy, other major disease</td>
<td>INH given within 10 minutes before meals

Initial INH doses based on wt, meal size, time of day, recent or anticipated exercise. Dose can be increased or decreased by 1mg based on SMBG or in anticipation for meals that were larger or smaller than usual or on an prn basis

Rosiglitazone doses were not adjusted

SMBG to be performed before meals and at bedtime

Target pre-meal glucose of 80-140mg/dl and bedtime value of 100-160mg/dl</td>
<td>TC (mg/dl): 195.3 ± 38.3/ 199.9 ± 49.9
HDL-C (mg/dl): 36.1 ± 8.7/ 40.1 ± 10.6
LDL-C (mg/dl): 116.3 ± 31.8/ 119.4 ± 29.5
TG (mg/dl): 224.1 ± 193.8 / 194.3 ± 147.8

Mean ± SD
Mean (range)</td>
<td>
<table>
<tr><td>% achieving HbA1c < 6.5%</td><td>28%</td><td>7.5%</td><td>Adjusted odds ratio 5.34[1.83-15.57]</td></tr>
<tr><td>HbA1c (%)</td><td>-2.3%</td><td>-1.4%</td><td>-0.89% [-1.23, -0.55]</td></tr>
<tr><td>Mean HbA1c (%)</td><td>7.2%</td><td>8.0%</td><td></td></tr>
<tr><td>FPG (mg/dl)</td><td>-64</td><td>-56</td><td>-4mg/dl[-18, 9]</td></tr>
<tr><td>2-h PPG (mg/dl)^</td><td>-92</td><td>-92</td><td>-4mg/dl[-18, 26]</td></tr>
<tr><td>Weight (kg)</td><td>+1.9</td><td>+0.8</td><td>0.95kg [-0.18, 2.09]</td></tr>
<tr><td>Hypoglycemia (events/pt-mo)</td><td>0.7</td><td>0.05</td><td>Risk ratio 14.72 [7.51, 28.83]</td></tr>
<tr><td>Severe hypoglycemia</td><td>0</td><td>0</td><td></td></tr>
<tr><td>Hypoglycemia (# episodes/ # pts.</td><td>153/36</td><td>9/5</td><td>0.95kg [-0.18, 2.09]</td></tr>
<tr><td>mean daily dose at week 12</td><td>15.3mg</td><td>not shown</td><td></td></tr>
<tr><td>Cough (%)</td><td>8%</td><td>1.5%</td><td></td></tr>
</table>
*p=0.0003
^2-h PPG done following a standardized meal
</td>
</tr>
<tr>
<td>Rosenstock 2005[10]
Phase III trial
R, OL, PR
USA and Canada
Duration: 3-months
<table>
<tr><th></th><th>I/O (n)</th><th>I (n)</th><th>O (n)</th></tr>
<tr><td>R</td><td>103</td><td>104</td><td>102</td></tr>
<tr><td>ITT</td><td>100</td><td>102</td><td>96</td></tr>
</table>
Superiority study design
ITT-LOCF analysis</td>
<td>Type 2 DM≥ 1 year
35-80 years old
≥ 2 months of stable treatment with therapeutic doses of combination therapy (SU or repaglinide + metformin or TZD)
HbA1c 8-11%

Exclusions: BMI > 35mg/kg^2, poorly controlled asthma, COPD, other significant respiratory disease, smoked in the last 6 months, abnormal EKG, DL_{CO} <75%, TLC <80% or >120%, FEV1 < 70% pred., use of systemic steroids, ≥2 severe hypoglycemic episodes in past 6 mos., hospitalization/ER visit due to poor DM control in past 6 mos., pregnancy, other major disease, abnormalities on lab screening</td>
<td>INH + existing OHA
vs.
INH alone
vs.
existing OHA

INH given within 10 minutes before meals (1-2 inhalations of 1or 3mg)

Initial INH doses based on wt, meal size, time of day, recent or anticipated exercise. Dose can be increased or decreased by 1mg based on SMBG or in anticipation for meals that were larger or smaller than usual or on a PRN basis.

inhaled insulin can also be administered with afternoon snack or at bedtime if warranted by SMBG results

doses of OHA were not adjusted during the study</td>
<td><u>Values for INH + OHA/ INH/ OHA</u>
% male: 64/ 72/ 61
Age (years): 58.3 ± 8.6 / 57.4 ± 9.2/ 56.4 ± 10
Duration of DM (years): 9.8(1-37) / 9.3 (1.8-25)/ 9.6 (1.3-32.8)
HbA1c (%): 9.48 ± 0.94/ 9.58 ± 0.87/ 9.56 ± 1.01
FPG (mg/dl): 195 ± 49/ 203 ± 43/ 203 ± 44
BMI (kg/m^2): 29.9 ± 3.7/ 30.2 ± 3.8/ 30 ± 4.0
Weight (kg): 88.9 ± 15.4/ 90 ± 15.6/ 87.9 ± 14.7
TC (mg/dl): 192 ± 37/ 193 ± 39/ 187 ± 40
HDL-C (mg/dl): 40 ± 11/ 40 ± 11/ 38 ± 11
LDL-C (mg/dl): 112 ± 31/ 116 ± 32/ 107 ± 31
TG (mg/dl): 203 ± 130 / 188 ± 110/ 213 ± 157
% using metformin: 90/ 87/ 90 (mean dose ~ 2100mg/d)
% using glyburide: 58/ 65/63 (mean</td>
<td>
<table>
<tr><th></th><th>INH + OHA</th><th>INH only</th><th>OHA only</th></tr>
<tr><td>Completed study (n)</td><td>99</td><td>97</td><td>93</td></tr>
<tr><td>HbA1c (%)</td><td>-1.9%*</td><td>-1.4%^</td><td>-0.2%</td></tr>
<tr><td>% achieving HbA1c < 8%</td><td>86%*</td><td>55.9%*</td><td>18.8%</td></tr>
<tr><td>% achieving HbA1c < 7%</td><td>32%</td><td>16.7%</td><td>1.0%</td></tr>
<tr><td>FPG (mg/dl)</td><td>-53 ± 4</td><td>-23 ± 4</td><td>1 ± 5</td></tr>
<tr><td>2-h PPG (mg/dl)</td><td>-79 ± 6</td><td>-66 ± 6</td><td>-3 ± 7</td></tr>
<tr><td>Hypoglycemia (events/pt-month)</td><td>1.7</td><td>1.3</td><td>0.1</td></tr>
<tr><td>Hypoglycemia (# episodes/ # pts.</td><td>477/78</td><td>365/69</td><td>13/8</td></tr>
<tr><td>Severe hypoglycemia</td><td>0</td><td>n=1</td><td>0</td></tr>
<tr><td>weight (kg)</td><td>2.7</td><td>2.8</td><td>0</td></tr>
<tr><td>Cough</td><td>12%</td><td>14%</td><td>2%</td></tr>
<tr><td>Mean daily dose at week 12</td><td>13.1 ± 8.5</td><td>26.4 ± 13.3</td><td>-</td></tr>
</table>
*tx group difference for OHA only and INH + OHA -1.67[95%CI-1.90, -1.44] p<0.001
^tx group difference for OHA only and INH only -1.18[95%CI -1.41, -0.95] p< 0.001
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<td>SMBG to be performed before meals and at bedtime

Target pre-meal glucose of 80-140mg/dl and bedtime value of 100-160mg/dl</td>
<td>dose ~ 19mg/d)
% using glipizide: 27/ 23/26 (mean dose ~ 20mg/d)

Mean ± SD
Mean (range)</td>
<td></td>
</tr>
<tr>
<td>Barnett 2006[30, 33]
Phase III trial
R, OL, PR

Duration: 24-weeks

<table>
<tr><th></th><th>SU+ INH (n)</th><th>SU + MET (n)</th></tr>
<tr><td>R</td><td>225</td><td>202</td></tr>
<tr><td>ITT</td><td>214</td><td>196</td></tr>
<tr><td>PP</td><td>190</td><td>171</td></tr>
</table>
Designed to show superiority in the high stratum arm and non-inferiority in the low stratum arm

ITT population defined as all randomized patients with a baseline A1c and at least on post-baseline value</td>
<td>Type 2 DM diagnosed at least 6 months before screening
35-80 years old
HbA1c 8-12% on maximal dose of a SU for at least 2 months before screening
DLco ≥ 75%
TLC 80-100%
FEV1 ≥ 70% predicted

Exclusions: moderate-severe asthma or COPD, clinically significant CXR abnormalities, smoking within 6 months of randomization, other agents that may affect glycemic control, C-peptide ≤ 2.0 nmol/l, major organ system disease, abnormal labs, pregnancy, lactation</td>
<td>4-week run-in period

Prior to randomization, patients were divided into low (8-9.5%) and high (>9.5- ≤ 12%) A1c stratums

SU + INH vs. SU + metformin

Initial INH dose based on weight and degree of glycemic control

Dose adjusted based to achieve FBG 80-140mg/dl using SMBG

Dose can be increased or decreased by 1mg based on SMBG or in anticipation for meals that were larger or smaller than usual or on a PRN basis.

Metformin was begun at 500mg once daily and titrated to 1gm BID</td>
<td><u>Results for SU + INH/ SU + metformin</u>
% male: 55%/ 51%
Age (years): 60.8/ 60
Weight (kg): 80.3/ 81.1
BMI (kg/m^2): 28.5/ 29.1
DM duration (years): 9.6/ 8.8
HbA1c (High stratum): 10.51%/ 10.62%
HbA1c (Low stratum): 8.8%/ 8.75%
FPG (mg/dl): 238.4/ 230.7</td>
<td>
<table>
<tr><th></th><th>SU + INH</th><th>SU + metformin</th><th>Treatment diff [95% CI]</th></tr>
<tr><td>Completed study (n)</td><td>206</td><td>175</td><td></td></tr>
<tr><td>HbA1c (%)
High stratum
Low stratum</td><td>
-2.2
-1.9</td><td>
-1.8
-1.9</td><td>
-0.38 [-0.63, -0.14]*
-0.07 [-0.33, 0.19]</td></tr>
<tr><td>HbA1c < 8%
High stratum
Low stratum</td><td>
48.7%
81.2%</td><td>
44.7%
73.1%</td><td>
1.11 [0.64, 1.93]
1.78 [0.86, 3.69]</td></tr>
<tr><td>HbA1c < 7%
High stratum
Low stratum</td><td>
20.4%
30.7%</td><td>
14.6%
32.3%</td><td>
1.45 [0.69, 3.01]
0.96 [0.51, 1.79]</td></tr>
<tr><td>FPG (mg/dl)
High stratum
Low stratum</td><td>
-46
-48</td><td>
-47
-52</td><td>
1[-11, 12]
4[-8, 16]</td></tr>
<tr><td>2-h PPG (mg/dl)^</td><td>162.9</td><td>171.7</td><td></td></tr>
<tr><td>Weight (kg)
High stratum
Low stratum</td><td>
+3.6
+2.4</td><td>
0
-0.3</td><td>
3.6 [2.81, 4.39]
2.67 [1.84, 3.51]</td></tr>
<tr><td>Mean daily dose at week 24</td><td>12.1mg (INH)</td><td>1g bid (metformin)</td><td></td></tr>
<tr><td>Hypoglycemia (events/pt-mo.)</td><td>0.31</td><td>0.17</td><td>Risk ratio 1.86 [1.56, 2.22]</td></tr>
<tr><td>Cough</td><td>9.0%</td><td>1.5%</td><td></td></tr>
</table>
*Significant vs. SU + metformin
^calculated using SMBG measurements
</td>
</tr>
<tr>
<td>Study 1002[30]
Phase III trial
R, OL, PR
Duration: 24-weeks

<table>
<tr><th></th><th>Met/ +INH (n)</th><th>Met/ SU (n)</th></tr>
<tr><td>R</td><td>243</td><td>233</td></tr>
<tr><td>ITT</td><td>234</td><td>222</td></tr>
</table>
</td>
<td>Type 2 DM diagnosed at least 6 months before screening
Treatment with metformin ≥ 1.5g/day for ≥ 2 months
HbA1c 8-12%</td>
<td>INH + metformin vs. SU + metformin

Glyburide was dosed at 2.5mg once daily to a maximum of 15mg daily</td>
<td><u>Results for Metformin + INH / Metformin + SU</u>

<u>High stratum (HbA1c >9.5-<12.5%)</u>
HbA1c (%): 10.4/ 10.6
FPG (mg/dl): 223/ 243
Weight (kg): 88.3/ 87.8

<u>Low stratum (HbA1c >8-<9.5%)</u>
HbA1c (%): 8.6/ 8.7
FPG (mg/dl): 187/ 196</td>
<td>
<table>
<tr><th></th><th>Metformin + INH</th><th>Metformin + SU</th><th>Treatment diff [95% CI]</th></tr>
<tr><td>Completed study (n)</td><td>219</td><td>205</td><td></td></tr>
<tr><td>HbA1c (%)
High stratum
Low stratum</td><td>
-2.2
-1.8</td><td>
-1.9
-1.9</td><td>
-0.37 [-0.62, -0.12]
-0.04 [-0.19, 0.27]</td></tr>
<tr><td>HbA1c < 8%
High stratum</td><td>
72.5%</td><td>
56.3%</td><td></td></tr>
</table>
</td>
</tr>
</table>

PP 215 207 Designed to show superiority in the high stratum arm and non-inferiority in the low stratum arm			Weight (kg): 90.3/ 88.2	Low stratum 80.8% 86.6% HbA1c < 7% High stratum 33.9% 17.5% Low stratum 40.0% 42.9% FPG (mg/dl) High stratum -42 -40 -2 [-14, 10] Low stratum -46 -49 4[-7, 15] Weight (kg) High stratum +2.8 +2.5 0.26 [-0.7, 1.21] Low stratum +2.0 +1.6 0.38 [-0.52, 1.27] Hypoglycemia* High stratum 0.2 0.1 Low stratum 0.2 0.2 *events/patient-month

Appendix 3: Pulmonary function tests (see page 23 for list of abbreviations used)

Treatments	Diabetes	n	Duration of study	FEV1	FVC	TLC	DLco
Weiss[8] • INH + oral agents • Oral agents	Type 2	32 36	12-weeks	-0.09 L -0.03 L	• -0.07 L • -0.02 L	• 0.02 L • 0.05 L	• -1.10 ml/min/mmHg • -1.26 ml/min/mmHg
Skyler [4] • INH + ultralente • Regular + NPH	Type 1	35 37	12-weeks	• -5.23% • -6.77%	• -4.77% • -1.5%	• +8.36% • +9.49%	• -11.43% • -7.71%
DeFronzo[9] • INH only • Rosiglitazone only	Type 2	75 68	12-weeks	• -0.016L • -0.001L adjusted difference -0.016 [-0.079 to 0.046]	• 0.002L • 0.009L adjusted difference -0.006 [-0.088 to 0.076]	• 0.033L • 0.064L adjusted difference -0.030 [-0.213 to 0.152]	• -0.973 ml/min/mmHg • -0.829 ml/min/mmHg adjusted difference -0.144 [-1.081 to 0.792]
Rosenstock[10] • INH + OHA • INH only • OHA only	Type 2	103 104 99	12-weeks	• -0.12 ± 0.02 L • -0.10 ± 0.02L • -0.07 ± 0.02 L Adjusted difference for (combination – OHA) -0.05 [-0.11 to 0.01] Adjusted difference for (INH – OHA) -0.03[-0.09 to 0.03]	• -0.10 ± 0.03 L • -0.06 ± 0.03 L • -0.05 ± 0.03 L Adjusted difference for (combination – OHA) -0.05 [-0.12 to 0.02] Adjusted difference for (INH – OHA) -0.01[-0.09 to 0.06]	• -0.11 ± 0.05L • -0.04 ± 0.05L • -0.05 ± 0.05L Adjusted difference for (combination – OHA) -0.06 [-0.19 to 0.07] Adjusted difference for (INH – OHA) 0.01[-0.12 to 0.14]	-1.17 ± 0.31 ml/min/mmHg -1.2 ± 0.32 ml/min/mmHg -0.46 ± 0.34 ml/min/mmHg Adjusted difference for (combination – OHA) -0.70 [-1.56 to 0.16] Adjusted difference for (INH – OHA) -0.73[-1.60 to 0.13]
Hollander[11] • INH + ultralente • Regular + NPH	Type 2	149 149	24-weeks	Adjusted mean difference 0.000L [-0.048 to 0.048]	Adjusted mean difference 0.025L [-0.041 to 0.090]	Adjusted mean difference 0.044L [-0.080 to 0.168]	Adjusted mean difference -0.403 [-1.166 to 0.360] units as ml/min/mmHg

Barnett[33] • INH +SU • Metfornin +SU	Type 2		24-weeks	Adjusted mean difference -0.07L [-0.12, -0.03]	Adjusted mean difference -0.06L [-0.11, -0.01]	Adjusted mean difference -0.04L [-0.19, 0.11]	Adjusted mean difference -0.32 [-1.10, 0.46] Units as ml/min/mmHg
Quattrin[5] • INH + ultralente • Regular + NPH	Type 1		24-weeks	Adjusted mean difference -0.031L [-0.082, 0.020]	Adjusted mean difference -0.018L [-0.080, 0.045]	Adjusted mean difference -0.087L [-0.211, 0.037]	Adjusted mean difference -1.218 [-1.95, -0.485] units as ml/min/mmHg
Skyler[6] • INH + NPH • Regular + NPH	Type 1	163 165	24-weeks	• -0.016 ± 0.256L • 0.008 ± 0.244L Adjusted mean difference -0.037 [-0.084, 0.010]	• 0.029 ± 0.309L • 0.022± 0.270 Adjusted mean difference -0.007 [-0.060, 0.046]	• 0.047 ± 0.522 L • 0.083 ± 0.543L Adjusted mean difference -0.058 [-0.161, 0.045]	• -0.750 ml/min/mmHg • -0.229 ml/min/mmHg Adjusted mean difference -0.791 ml/min/mmHg [-1.4661, -0.117]
Barnett[13] • INH + SU or metformin • SU + metformin	Type 2	336 291	1-year	Adjusted difference -0.05 L	Not evaluated	Not evaluated	Adjusted difference -0.01ml/min/mmHg
Rosenstock[12] • Inhaled to inhaled • Inhaled to SQ • SQ to SQ • SQ to inhaled	Type 1 and 2	44 6 13 39	1-year	• -0.03 ± 0.22 L • 0.02 ± 0.08 L • 0.02 ± 0.35 L • -0.05 ± 0.16 L mean ± SD	Not evaluated	Not evaluated	• -1.05 ± 4.69 • -1.51 ± 4.68 • -2.53 ± 4.82 • -2.50 ± 6.95 Units as ml/min/mmHg mean ± SD
Dreyer[34] • INH + SU or metformin • SU + metformin	Type 2	158 146	2-year	• -0.170L • -0.128L adjusted difference -0.039 ± 0.028 [-0.093, 0.015]	Not evaluated	Not evaluated	• -1.529 • -1.583 Adjusted difference 0.112 ± 0.392 [-0.655, 0.880] Units as ml/min/mmHg
Cefalu[14] uncontrolled extension trials w/ inhaled insulin	Type 2	384	2-years	-0.074 L [-0.084, -0.063]	Not evaluated	Not evaluated	-0.634 [-0.816, -0.452] units as ml/min/mmHg/yr
Skyler[15] Inhaled insulin	Type 1 and 2	89	4-years	-0.057 ± 0.004L/yr (INH from 4-yr data) -0.071 ± 0.023 (non-INH users from 2-yr data) Mean ± SE	Not evaluated	Not evaluated	-0.376 ± 0.067(INH from 4-yr data) -0.673 ± 0.423(non-INH users from 2-yr data) Units as ml/min/mmHg/yr Mean ± SE

Abbreviations used in appendices

BMI= body mass index; COPD= chronic obstructive lung disease; CXR= chest X-ray; DLco= diffusing capacity of carbon dioxide; DM= diabetes mellitus; EKG= electrocardiogram; FEV1= forced expiratory volume in 1 second; FPG= fasting plasma glucose; FVC= forced vital capacity; HTN= hypertension; INH= inhaled insulin; ITT= intent-to-treat; LOCF=last observation carried forward; OHA =oral hypoglycemic agents; OL= open label; PFTs= pulmonary function tests; PPG= postprandial glucose; PR= parallel; R= randomized; SCr=serum creatinine; SMBG= self-monitoring of blood glucose; SQ= subcutaneous; TLC= total lung capacity